REMARKS

Claims 17-19 have been canceled. Claims 11-16 and new Claims 20-22 are active in the case. Reconsideration is respectfully requested.

The present invention is directed to piperazinylbenzothiazole compounds that are useful in the treatment of cerebral ischemic disorders and CNS disorders.

Claim Amendments

Claims 11-16 have been amended in order to improve upon the form of the claims. None of the amendments are believed to have introduced new matter into the case. Entry of the amendments into the record is respectfully requested.

Rejections, 35 USC 112 & 35 USC 101

Claims 1-16 have been amended to a form which is believed to be satisfactorily sufficient to resolve the issues that have been raised with respect to these claims.

Claims 17 and 18 have been canceled in favor of new Claims 20 and 22 which place the subject matter of the canceled claims in proper composition and method-of-use format.

Claim 19 has been canceled in favor of new Claim 22 which places the process of producing the claimed piperazinyl benzothiazole compound in proper process claim format. Entry of the amendments and new claims into the record is respectfully requested. Withdrawal of the rejections of the claims is respectfully requested.

Rejection of Claims 17 & 18, 35 USC 112, First Paragraph

Claims 17 and 18 have been rejected for the reason that the subject matter of these claims is not believed to be sufficiently enabled by the disclosure of the specification. The Examiner maintains that the present specification does not contain sufficient information for

one of skill in the art to fully practice the invention by utilizing the claimed piperazinyl benzothiazoyl compound in the treatment of cerebral ischemia and CNS disorders. Applicants do not concur with the opinion of the Examiner. The present specification in the first several pages clearly discusses what is known as the JNK signaling pathway which is activated by exposure of cells to environmental stresses such as chemical toxins, radiation, hypoxia and osmotic shock, as well as treatment of cells with growth factors or pro-inflammatory cytokines. Once activated, JNK binds to the N-terminal region of transcription factor targets and phosphorylates the transcriptional activation domains resulting in the up-regulation of expression of various gene products, which can lead to apoptosis, inflammatory responses or oncogenic processes. It is known that activation of the JNK pathway in a number of disease processes provides a rational for targeting this pathway by the administration of effective drugs.

Auto-immune and inflammatory diseases result from the inappropriate activation of the immune system. Activated immune cells express many genes that encode inflammatory molecules such as cytokines, growth factors, cell surface receptors, cell adhesion molecules and degradative enzymes. Many of the genes are known to be regulated by the JNK pathway.

The JNK signaling pathway, and especially that of JNK2 and JNK3, is thought by those of skill in the art to be implicated in a number of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, epilepsy and seizures, Huntington's disease, CNS disorders, traumatic brain injuries, as well as ischemic disorders and hemorrhaging strokes. Accordingly, research has led to the indication of several small molecules as modulators of the JNK pathway. One of such small molecules is the benzothiazole compound disclosed in WO '920, which has been cited of record against the present claims.

In view of the background discussed above as it pertains to the known JNK pathway, applicants submit that the disclosure in the present specification of a piperazinyl

benzothiazole compound, that is active as a JNK pathway inhibitor, is sufficiently enabling of the present invention. The present text clearly describes the scope of the structure of the present compound and how it can be produced. Further, the text on page 31 describes the methodology of a JNK2 and JNK3 *in vitro* assay in detail of the manner by which a compound can be tested as an inhibitor of JNK2 and JNK3, and then expressly states at the bottom of the page that tested compounds within the scope of the molecular structure shown in Claim 11 display an inhibition (IC_{50}) with respect to JNK3 of less than 10 μm, preferably less than 1 μm and more preferably less than 0.25 μm. Such a disclosure is entirely adequate for one of skill in the art to practice the present invention as in order to utilize the present piperazinyl benzothiazole compounds embodiments as inhibitors of the JNK pathway.

The disclosure of a second biological assay on pages 32 and 33 is directed to a method of determining global ischemia. A detailed description is provided of a procedure by which the ability of the present compound embodiments can be tested for JNK inhibiting capability in accepted animal test models (gerbils). A test compound of the present invention, i.e., the 1,3-benzothiazol-2-yl[2-({4-[(4-methylpiperazin-1-yl)methyl]benzyl}oxy)pyrimidin-4-yl]acetonitrile compound of Example 1, was tested and showed an inhibition of neuronal death of about 60 %. Accordingly, applicants submit that the test data presented in the specification is sufficiently enabling for one of skill in the art to practice the invention embodiments originally claimed in Claims 17 and 18, now Claims 20 and 21. Accordingly, the outstanding ground of rejection is believed to have been overcome and withdrawal of the same is respectfully requested.

Prior Art Rejection, 35 USC 103

Claims 11-19 stand rejected based on 35 USC 103 as obvious over Halazy et al, WO '920. This ground of rejection is respectfully traversed.

The cited reference discloses certain benzothiazole compounds that are characterized by having a benzothiazole-acetonitrile unit to which a substituted pyrimidyl unit is directly attached. Various compound embodiments within the scope of the basic structure are said to be inhibitors of JNK2 and/or JNK3, and a number of specific compound embodiments are disclosed on pages 14-18 of the document. A few compounds on page 14 contain a piperazinyl group as a component of the disclosed compound. However, here the piperazinyl groups are directly attached to the pyrimidinyl group of the disclosed basic structure of the pyrimidinyl benzothiazole compound. There is no teaching or suggestion of a 4-substituted piperazinylmethyl substituted phenoxy (benzyloxy or phenylethoxy) group that is attached to the 2 position of the pyrimidinyl component of the benzothiazole acrylonitrile unit. Accordingly, there is no suggestion of the compound as claimed in the present invention in the reference, and it is therefore believed that the obviousness ground of rejection fails. Withdrawal of the rejection is respectfully requested.

Obviousness-type Double Patenting Rejection

Claims 11-19 stand provisionally rejected over Claims 1, 3, 10-15, 28-30 and 43 of copending application Serial No. 10/168,718. This ground of rejection is respectfully traversed.

Since the rejection is a provisional rejection, applicants will take appropriate action in this case once patentable subject matter has been indicated in the copending application. Accordingly, the Examiner is requested to hold the rejection in abeyance until such notice.

It is now believed that the application is in proper condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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